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AMINOPHENOL DERIVATIVES AND THEIR USE IN COSMETICS
[Dérivés d'aminophénol et leur utilisation en cosmétique]
(Partial translation pp. 1-7)

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The present invention pertains to the use of aminophenol derivatives as depigmentation, or bleaching agents in a cosmetic, and/or dermatology compound, to a cosmetic, and/or dermatology compound containing these derivatives, and to new aminophenol derivatives. /1*

Human skin color is based on different factors, and in particular seasons of the year, race, and sex, and it is mainly determined by the nature, and the concentration of melanin produced by the melanocytes. Melanocytes are specialized cells, who synthesize melanin through the intermediary of special organelles, the melanosomes. In addition, at different periods in their life, certain people see darker, and/or more colored spots appear on the skin, and more especially the hands, giving the skin a certain heterogeneity. These spots are also due to a larger concentration of melanin in the keratocytes situated on the surface of the skin.

In the same way, the color of skin hair, and hair is due to melanin, when the skin hair, or hair is darker, some people wish to have them lighter. This is particularly interesting for the hairs which are less visible when they are light, than when they are dark.

The mechanism of the formation of the skin's, skin hairs', and hair's pigmentation, that is to say, the formation of the melanin

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*Numbers in the margin indicate pagination in the foreign text.

is particularly complex, and diagrammatically uses the following main steps:

Tyrosine--->Dopa--->Dopaquinone--->Dopachrome--->Melanin

The tyrosine (monophenol dihydroxyl phenylalanine: oxygen oxydo-reductase EC 1.14.18.1) is the main enzyme occurring in this chain of reactions. It catalyzes, in particular, the reaction of the transformation of the tyrosine into Dopa (dihydroxyphenylalanine), by means of its hydroxylase activity, and the transformation reaction of Dopa into dopaquinone, by means of its oxidase activity. This tyrosinase only acts when it is in the state of maturation under the action of certain biological factors.

A substance is recognized as being bleaching if it directly acts on the vitality of the epidermic melanocytes, where the melanogenesis occurs, and/or if it interferes with one of the steps in the biosynthesis of melanin, either by inhibiting one of the enzymes implicated in the melanogenesis, or by placing itself as a base analogue of one of the chemical compounds of the melanin synthesis chain, chain which can then be blocked,and thus ensure depigmentation.

The substances most used as depigmentation agents are more especially hydroquinone, and its derivatives, in particular its ethers, like hydroquinone monomethylether, and monoethylether. There compounds, although they have a certain effectiveness, are unfortunately not free from side effects because of their toxicity,

which can make their use difficult, even dangerous. This toxicity comes form the fact that they act on the fundamental mechanisms of the melanogenesis, by killing the cells which then risk to disturb /2 their biological environment, and which, consequently, oblige the skin the expel them by producing toxins.

Thus, hydroquinone is a particularly irritating, and cytotoxic compound for the melanocyte, whose total, or partial replacement has been envisioned by many authors.

Thus, one has searched for substances which do not intervene in the melanogenesis mechanism, but which act before on the tyrosinase, by preventing its activation, and are much less toxic because of this. Kojic acid, which complexes the copper present in this enzyme's active site, is habitually used as an inhibitor of the tyrosinase activation. Unfortunately, this compound can cause allergic reactions ("Contact allergy to kojic acid in skin care products", Nakagawa M. et al., in Contact Dermatitis, Jan. 95, Vol 42 (1), pp. 9-13). This compound is also unstable in a solution, which somewhat complicates manufacturing the compound.

The use of inoffensive, topical depigmentation substances, having good effectiveness, is most particularly sought after in order to treat regional hyperpigmentations through melanocyte hyperactivity, such as idiopathic melasma, occurring during pregnancy ("pregnancy mask", or chloasma), or from a combination oral contraceptive, localized hyperpigmentations by benign,

melanocyte proliferation, and hyperactivity, such as old age pigmentary spots, called actinic lentigo, accidental hyperpigmentations, or depigmentations, eventually due to photosensibilization, or post-lesion scaring, as well as certain leucodermias, such as vitiligo. For these last ones (scaring which can end with a scar giving the skin a whiter aspect, and leucodermias), not being able to repigment the damaged skin, one can succeed in depigmentizing the residual normal skin areas, in order to give all the skin a homogenous white tint.

Thus, the need subsists for a new agent for bleaching human skin, skin hairs, and/or hair, with as effective an action as the ones known, but not having any of their disadvantages, that is to say, non-irritating, non-toxic, and/or non-allergenic for the skin, and stable in a compound.

The Claimant has found, unexpectedly, that aminophenol derivatives have a depigmentation activity, even at weak concentrations, without revealing any cytotoxicity.

Some of these derivatives are already known from US-A-2 663 730, USA-A-3 933 470, GB-A-1 205 029, DD 107 449, or A. ETIENNE ET AL, "Dimethyl-1.3, and aryl-5 isocyanurates", Comptes rendus hebdomadaires des séances de l'académie des sciences, Série C: sciences chimiques, Vol. 279, 2 December 1974, pp. 969-972, for example. Other aminophenol derivatives have been discovered by the Claimant.

The present invention therefore pertains to the use of at least one aminophenol derivative with the following formula (I):

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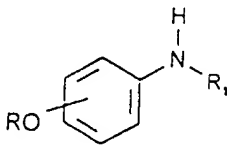


(I)

in which:

R represents a hydrogen atom, or a $-COR_2$ radical,

with R_2 representing a radical chosen from among an alkyl, or alkoxyl radical, saturated, or unsaturated, linear, cyclic, or branched, at C_1 to C_{30}, eventually hydroxylated,

R_1 is chosen from among a radical with the following formulas (a), (b), or (c):

(a) $-CO-NR_3R_4$

(b) $-CO-O-R_5$

(c) $-SO_2-R_5$

with R_3 representing a hydrogen atom, or a C_1 to C_6 alkyl radical, linear, or branched, saturated, or unsaturated, eventually hydroxylated,

with R_4 representing a hydrogen atom, or a radical chosen from among a C_1 to C_{30} alkyl radical, saturated, or unsaturated, linear, cyclic, or branched, eventually hydroxylated,

with R_5 representing a radical chosen from among an alkyl radical, saturated, or unsaturated, cyclic, or branched, in C_1 to C_{30}, eventually hydroxylated, in a cosmetic compound, depigmentizing, and/or bleaching human skin, skin hairs, or hair.

These compounds have the advantage of being easily obtained. In particular they can be obtained by having an aminophenol react with an activated chemical entity, like a imidazolide, or an isocyanate, when R_1 is a formula (a) radical, a chloroformiate, when R_1 is a formula (b) radical, or a sulfonyl chloride, when R_1 is a formula (c) radical.

According to the present invention, among the linear, or branched alkyl radicals with 1 to 30 carbon atoms, we can advantageously mention the methyl, ethyl, propyl, isopropyl, butyl, tertiobutyl, hexyl, octyl, nonyl, 2-ethyl-hexyl, and dodecyl radicals. Preferably, these radicals have 1 to 12 carbon atoms. Even more preferentially, the alkyl radical usually includes 1 to 6 carbon atoms. The methyl, ethyl, propyl, isopropyl, tertiobutyl, hexyl radicals can be mentioned as inferior alkyl radicals.

Among the linear alkyl radicals with 1 to 30 atoms, we can /4 mention in particular, the methyl, ethyl, propyl, octyl, dodecyl, tridecyl, hexadecyl, behenyl, octadecyl, tetracosyl, hexacosyl, octacosyl, and myricyl radicals.

Among the branched alkyl radicals with 1 to 30 carbon atoms, the 2-ethyl-hexyl, 2-butyl-octyl, 2-hexyl-decyl radicals can be

mentioned in particular.

When it is unsaturated, a radical with one, or several ethylene unsaturations, like the neryl, 2-nonyl 2 butenyl, 6-(1,3-pentadienyl)-2,4,7-dodecanetrien-9-ynyl radicals, is preferred, and most especially the allyl radical.

When the alkyl radical is cyclic, the cyclohexyl, cholesteryl, or terbutylcyclohexyl radical can be mentioned in particular.

When it is hydroxylated, the radical includes preferably 1 to 6 carbon atoms, and 1 to 5 hydroxyl groups.

Among the monohydroxyalkyl radicals, a radical containing preferably 1 to 3 carbon atoms, is preferred, in particular, the hydroxymethyl, 2-hydroxylethyl, 2, or 3-hydroxypropyl radicals.

Among the polyhydroxyalkyl radicals, a radical containing 3 to 6 carbon atoms, and 2 to 5 hydroxyl groups is preferred, such as the 2,3-dihydroxypropyl, 2,3,4-trihydroxybutyl, 2,3,4,5-tetrahydroxyepentyl, and 2,3,4,5,6-pentahydroxyhexyl radicals.

The alkoxylated radicals are the alkyl radicals, such as described above in particular, preceded by an oxygen atom.

Preferably, the aminophenol derivatives of the present invention are the ones for which at least one, and preferably all of the conditions below are met:

- R represents a hydrogen atom,
- the -OR function on the phenyl radical is at the ortho position, and advantageously, at the para position,

- R_1 is chosen from among a radical with formulas (a), or (b).

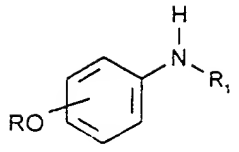
The formula (I) compounds are more especially chosen among N-ethyloxycarbonyl-4-amino-phenol, N-ethyloxycarbonyl-O-ethyloxycarbonyl-4-amino-phenol, N-cholesteryloxycarbonyl-4-amino-phenol, and N-ethylaminocarbonyl-4-amino-phenol.

The present invention also pertains to cosmetic, and/or dermatology compounds including at least one formula (I) aminophenol derivative, and a cosmetically, or dermatologically accepted medium. This compound is intended, in particular, for topical use on the skin, and/or its integuments (hair, skin hair, nails).

This cosmetic, and/or dermatology compound is advantageously /5 intended to depigmentize, and/or bleach human skin, and/or to remove pigmentary spots on the skin, and/or to depigmentize the skin hair, and/or hair.

The present invention also pertains to the use of these aminophenol derivatives in, and/or for manufacturing a cosmetic, and/or dermatology compound, as an inhibitor of tyrosinase, and/or the synthesis of melanin, and/or as a depigmentation, and/or bleaching agent of the skin, skin hair, or hair.

The present invention also pertains to the new formula (I) aminophenol derivatives below:



(I)

in which

R represents a hydrogen atom, or a $-COR_2$ radical,

with R_2 representing a radical chosen from among an alkyl, or alkoxyl radical, saturated, or unsaturated, linear, cyclic, or branched, at C_1 to C_{30}, eventually hydroxylated,

R_1 is chosen from among the following radicals:

(a) a $-CO-NR_3R_4$ radical

(b) a cholesteryloxycarbonyl radical

(c) an $-SO_2-R_5$ radical

with R_3 representing a hydrogen atom, or a C_1 to C_6 alkyl radical, linear, or branched, saturated, or unsaturated, eventually hydroxylated,

with R_4 representing a radical chosen from among a C_1 to C_{30} alkyl radical, saturated, or unsaturated, linear, cyclic, or branched, eventually hydroxylated, and

with R_5 representing a radical chosen from among an alkyl radical, saturated, or unsaturated, cyclic, or branched, in C_1 to C_{30}, eventually hydroxylated.

The present invention also pertains to a cosmetic process of depigmentation, and/or bleaching of the human skin, skin hair, or hair consisting of applying a cosmetic compound according to the invention on the skin, skin hair, or hair.

The compound according to the invention is suitable for topical use, and therefore contains a cosmetically, or dermatologically accepted medium, that is to say, compatible with the skin, skin hair, or hair.

The aminophenol derivatives will be used in an amount effective for obtaining the desired depigmentation, or bleaching effect, and this amount will be dependant on the nature of the aminophenol derivatives considered. In particular the formula (I) /6 aminophenol derivatives can be present in the compound, especially in an amount going from 0.001 to 10%, and preferably 0.005 to 5% of the compound's total weight.

The invention's compound can be presented in all the galenic forms normally used for a topical application, in particular in the form of an aqueous, hydroalcoholic, oily solution, an oil-in-water, or water-in-oil emulsion, or several, an aqueous, or oily gel, an anhydrous liquid, paste, or solid product, an oil dispersion in an aqueous phase by means of spheroids, these spheroids can be polymer nanoparticles, such as nanospheres, and nanocapsules, or better ionic, and/or non-ionic lipide droplets.

This compound can be more or less fluid, and have the aspect of a white, or colored cream, a pomade, a milk, lotion, serum, paste, foam. It can eventually be applied on the skin, or the hair in the form of an aerosol. It can also be presented in a solid form, and for example, in stick form. It can also be used as a treatment product, and/or makeup product. It can also be in the form of shampoo, or after-shampoos.

In the known manner, the invention's compound can also contain the additives which are usual in the cosmetic, and dermatology fields, such as hydrophilic, or lipophile gelling agents, preservatives, antioxidants, solvents, perfumes, fillers, filters, pigments, odor absorbers, and coloring materials. The amounts of these different additives are the ones conventionally used in the fields considered, and for example, 0.01 to 20% of the compound's total weight, These additives, according to their nature, can be incorporated in the oily phase, the aqueous phase, in the lipid droplets, and/or in the nanoparticles.

When the invention's compound is an emulsion, the proportion of the oily phase can go from 5 to 80% in weight, and preferably from 5 to 50% in weight in relation to the compound's total weight. The oils, emulsifiers, and co-emulsifiers used in the compound in the emulsion form are chosen from among the ones used conventionally in the field considered. The emulsifier, and co-emulsifier are present, in the compound, in a proportion going from

0.3 to 30% in weight, and preferably from 0.5 to 20% in weight in relation to the compound's total weight.

As oils which can be used in the invention, we can mention mineral oils (vaseline oil), oils of plant origin (avocado oil, soybean oil), oils of animal origin (lanolin), synthetic oils (perhydrosqualene), silicon oils (cylcomethicone), and fluorated oils (perfluoropolyethers). Fatty alcohols (cetylic alcohol), fatty acids, waxes (carnauba wax, ozokerite) can also be used as fats.

As emulsifiers, and co-emulsifiers that can be used in the /7 invention, we can mention, for example, fatty acid esters, and polyethylene glycol, like PEG-20 stearate, and the fatty acid esters, and glycerin, like glyceryl stearate.

As hydrophilic gelling agents, we can mention in particular the carboxyvinylic polymers (carbomer), the acrylic copolymers, like the acrylate/alkylacrylate copolymers, the polyacrylamides, the polysaccharides, natural gums, and clays, and as lipophilic gelling agents, we can mention modified clays, like the bentones, fatty acid metallic salts, hydrophobic silica, and polyethylenes.

As active agents, we can use in particular the polyols (glycerin, propylene glycol), vitamins, keratolytic, and/or desquamant agents (salicylic acid, and its derivatives), alpha-hydroxy acids, ascorbic acid, and its derivatives), anti-inflammatory agents, calming agents, and their mixtures. The

aminophenol derivatives can also be associated with other depigmentation agents, like kojic acid, or hydroquinone, and its derivatives, which enables using these latter ones in doses which are less toxic for the skin. In the case of incompatibility, these active agents, and/or aminophenol derivatives can be incorporated in spheroids, in particular ionic, or non ionic droplets, and/or the nanoparticles (nanocapsules, and/or nanospheres), in order to isolate them from each other in the compound.

The invention will now be illustrated by means of the following examples. The concentrations are given in percentage of weight.

[Translator's note: Requested translation ends here.]